B3 cont.

11. (Amended) The method according to claim 8, wherein the cytokine is granulocyte colony stimulating factor (G-CSF).

B4

13. (Amended) The method according to claim 10, wherein the cytokine is administered before blocking very late antigen-4 (VLA-4) [antigen] on the surface of the $CD34^+$ cells.

REMARKS

Applicant requests reconsideration of this application in view of the foregoing amendments and the following remarks.

Applicant has concurrently filed a Statement Under 37 C.F.R. § 1.821(f) to indicate that the content of the paper and computer readable copies for the sequence listings are the same.

Claims 1-14 stand rejected under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Examiner has raised several issues in making this rejection each of which is addressed below.

Referring to claim 1, the Examiner states:

> "In order to avoid possible confusion over proteins with the same or similar names and abbreviations that may be found to have patentably different structure and/or utility, the names of the proteins should be written out rather than abbreviated, i.e. VLA-4, VCAM-1, G-CSF, IL-1...

As suggested by the Examiner, applicant has written out the names of the proteins in the amended claims.

The Examiner asserts that "it is not known as to what is involved in 'peripheralizing $CD34^+$ cells' and the specification does not provide a clear definition for the term, 'peripheralization'." Applicant traverses.

Applicant has clearly defined "peripheralization" as a method for increasing the number of stem cells and $CD34^+$ cells

in peripheral blood. See, e.g., page 8 (first paragraph) of the specification. Accordingly, this rejection should be withdrawn.

Referring to claim 2, the Examiner states that "the list of blocking agents is confusing." Applicant has amended claim 2, taking into account the Examiner's suggestions, to overcome this rejection. Applicant has also inserted the word "and" before the phrase "Fab, Fab', $F(ab')_2$ or F(v) fragments thereof" to indicate that the blocking agent may be an anti-VLA-4 antibody, human, chimeric or humanized anti-VLA-4 antibody and fragments of such anti-VLA-4 antibodies.

Referring to claim 3, the Examiner states:

> "the phrase, 'at least a portion of the $CD34^+$ cells are hematopoietic stem cells', is vague and indefinite. It is unclear as to what percentage of [the $CD34^+$ cells] must be hematopoietic stem cells in order for peripheralization to proceed efficiently."

Applicant has cancelled this claim and dependent claims 6, 9. and 12 without prejudice to obviate this rejection.

Claims 1-14 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner states: "... the disclosure is enabling only for claims limited to the blocking agent, anti-VLA-4 antibody and the cytokine, GM-CSF [sic]." More specifically, the Examiner asserts:

> The specification does not adequately teach peripheralizing $CD34^+$ cells using fibronectin, soluble VCAM-1, Fab fragments of the anti-VLA-4 antibody, or peptides and variants thereof. Although these blocking agents are known to interfere with binding of $CD34^+$ cells to the stromal cells <u>in vitro</u>, applicant has not shown that these agents are capable of blocking VLA-4 antigen and peripheralizing $CD34^+$ cells <u>in vivo</u>. While data from <u>in vitro</u> assays are useful in screening for potentially useful agents, one cannot simply extrapolate the data to an <u>in vivo</u> system. The success of the claimed method is dependent on adequate concentrations of the agent reaching the desired site <u>in vitro</u> [sic]. There are many properties of these agents such as half-life, deactivation by the liver, rapid excretion, adverse side effects, etc. that cannot be ascertained by <u>in vitro</u> experiments.
>
> Likewise, applicant has not provided evidence that other cytokines can peripheralize $CD34^+$ cells <u>in vivo</u>. Though G-CSF is successful in peripheralizing

> $CD34^+$ cells *in vivo*, it is not known whether the other cytokines are suitable for *in vivo* use for reasons previously discussed.
>
> Thus, it would require undue experimentation of one of ordinary skill in the art to use the embodiments of the invention as claimed.

Applicant traverses.

Applicant's amended claims are directed to methods of peripheralizing $CD34^+$ cells by blocking VLA-4 present on the surface of those cells.* Applicant has demonstrated, by way of an *in vivo* example, that blocking VLA-4 on $CD34^+$ cells results in peripheralization of $CD34^+$ cells. In the illustrative experiment, applicant used a monoclonal antibody which binds to VLA-4 and blocks the interaction between VLA-4 and its known ligands (i.e., VCAM-1 and fibronectin). Having demonstrated that blocking of the VLA-4 on the surface of $CD34^+$ cells results in peripheralization, applicant is entitled to claim methods which utilize fragments of blocking antibodies and other molecules also known to block VLA-4.

Likewise, having demonstrated that G-CSF, a growth factor known to stimulate proliferation of stem cells, when used in combination with a blocking agent causes a dramatic increase in peripheralization of $CD34^+$ cells *in vivo*, applicant is entitled to claim methods that use other growth factors also known to cause proliferation of stem cells. This is especially the case, when the growth factors recited in applicant's claims have been previously used *in vivo* and shown to stimulate stem cell proliferation. See, e.g., pages 16 and 17 of the specification.

Accordingly, the ordinary skilled artisan would be able to practice all of the claimed embodiments without undue

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* Applicant has defined "blocking VLA-4 antigens" as interfering with interactions between VLA-4 antigens and either VCAM-1 or fibronectin on the surface of stromal cells or in the extracellular matrix. See, page 12, second paragraph of the specification.

experimentation and would reasonably expect them to be successful. Therefore, the rejection of the pending claims under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Claims 1-14 stand rejected under 35 U.S.C. § 103 "as being unpatentable over Haas et al. or Craig et al. in view of Anklesaria et al. or Williams et al.*" Applicant traverses.

As demonstrated below, the amended claims of the instant application are not obvious over the documents cited by the Examiner. Specifically, there is no suggestion in those documents that would prompt an ordinary skilled artisan to combine the teachings of the documents or to modify those teachings in the manner suggested by the Examiner. It is also evident from the discussion below that the Examiner has not met the burden of establishing a prima facie case of obviousness. See, e.g., In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1783 (Fed.Cir. 1992) (copy attached):

> "'Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so.' Although couched in terms of combining teachings found in the prior art, the same inquiry must be carried out in the context of a purported obvious 'modification' of the prior art. The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification. (Emphasis in original; citations omitted.)

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* A Notice of References Cited by Examiner (PTO-892) was not attached to the Office Action of June 29, 1993. Therefore, applicant assumes that the four documents cited by the Examiner correspond to documents listed in applicant's Information Disclosure Statement (IDS) of February 13, 1993. The only document listed in that IDS with Anklesaria as the lead author was incorrectly cited as:

> Anklesaria and Teixido, Blood 78: Suppl. 1, p. 302a, abstract 1200 (1991).

The correct citation for this reference is:

> Teixido et al., Blood 78: Suppl. 1, p. 302a, abstract 1200 (1991).

Apposite also is In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed.Cir. 1992) (copy enclosed):

> "If examination at the initial stage does not produce a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent."

The crux of applicant's invention, which is embodied in amended claim 1, the only independent claim pending in this application, is that blocking of VLA-4 on the surface of $CD34^+$ cells leads to peripheralization of $CD34^+$ cells. The amended claims all recite a method for doing just that. The documents cited by the Examiner nowhere disclose or suggest such method. They do not teach that peripheralization of $CD34^+$ cells may be accomplished by blocking VLA-4. Therefore, claim 1 and all the other pending claims are patentable.

Teixido states that the in vitro adhesion of cells expressing high levels of CD34 to monolayers of cultured bone marrow cells is 40% inhibited by an anti VLA-4 antibody. This document, contrary to the Examiner's views, does not teach the use of VLA-4 ligands to block the adhesion of $CD34^+$ cells to stroma. It merely states that "wells coated with sVCAM supported $CD34^+$ cell adhesion which was completely inhibited by [anti-VLA-4 antibody]" and that "adhesion to FN40 [the CS-1 site in an alternately spliced region of fibronectin] was weak." Nowhere does Teixido disclose or suggest that the number of hematopoietic stem cells in the peripheral blood may be increased by blocking VLA-4 on the surface of $CD34^+$ cells.

Williams states that monoclonal antibodies against VLA-4 block adhesion of CFU-S_{12} stem cells to fibronectin coated plates. It also states that the in vitro incubation of bone marrow cells with rabbit polyclonal antibodies against integrin β_1, prior to intravenous administration into lethally irradiated mice, caused a reduction in the ability of the

injected marrow cells to give rise to spleen colonies or myeloid colonies. From this observation, Williams concluded:

> "... the adhesion of primary haematopoietic stem cells to stromal cell ECM is partly promoted by the proteolytic fragments of fibronectin containing the alternatively spliced region of the IIICS domain and we suggest that this interaction is likely to be mediated by the integrin receptor VLA-4 (α_4/β_1). ... These interactions may have important implication in the localization of intravenously injected stem cells to the medullary cavity during bone marrow transplantation and modulation of expression of VLA-4 may have a role in loss of adhesion of leukaemic blast cells to stromal cells noted during blast crisis in chronic myelogenous leukaemia. By analogy to lymphocyte homing mechanisms, stem-cell stromal interactions may use multiple ligand-receptor interactions including VLA-4/CS-1 described here and lectins described previously."

Williams, based on in vitro data, also speculates that VLA-4 may be involved in the binding of stem cells to the bone marrow microenvironment. And Williams suggests that the in vitro pre-treatment of stem cells with anti integrin β_1 antibodies may prevent these cells from homing (i.e., reaching and attaching to the medullary cavity of bone marrow or forming colonies in the spleen). Nowhere, however does Williams teach, as asserted by the Examiner, that blocking the VLA-4 on $CD34^+$ cells will lead to inhibition of adhesion of hematopoietic stem cells to the stroma (i.e., homing) and their release from the bone marrow into the peripheral blood (i.e., peripheralization). The Examiner's interpretation -- an assumption that methods of inhibiting homing will also cause peripheralization of stem cells already residing in their bone marrow microenvironment -- requires a giant leap of faith. Yet, none of the cited documents support such leap.

Haas refers to the increase in the number of circulating progenitor cells in cancer patients who were administered recombinant human GM-CSF. Haas does not disclose or suggest that blocking VLA-4 would cause peripheralization of $CD34^+$ cells.

Craig is a review article on peripheral blood stem cell transplantation (PBST). Craig refers to the use of recombinant growth factors to mobilize stem cells. Nowhere does Craig disclose or suggest peripheralization of $CD34^+$ cells by blocking VLA-4.

Therefore, it is applicant and not the prior art that discloses peripheralization via blocking of VLA-4. And, the Examiner's contention to the contrary is hindsight. Such hindsight reconstruction, however, has been proscribed by the CAFC:

> "It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated '[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'"

In re Fritch, 972 F.2d at 1266, 23 USPQ2d at 1783 (citations omitted).

For all of the foregoing reasons, applicant requests the Examiner to enter the above amendments, to reconsider the objections and rejections, and to allow the claims of this application, as amended. If the Examiner believes that an interview would facilitate the resolution of any outstanding issue, the Examiner is requested to contact the undersigned.

Respectfully submitted,

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